

# UC Irvine

## UC Irvine Previously Published Works

### Title

Not lost to follow-up: A rare case of CHILD syndrome in a boy reappears.

### Permalink

<https://escholarship.org/uc/item/8w34q4cp>

### Journal

JAAD case reports, 4(10)

### ISSN

2352-5126

### Authors

Fackler, Nathan  
Zachary, Cameron  
Kim, Dong Joo  
et al.

### Publication Date

2018-11-01

### DOI

10.1016/j.jdcr.2018.10.001

### Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

# Not lost to follow-up: A rare case of CHILD syndrome in a boy reappears



Nathan Fackler, MS,<sup>a,b</sup> Cameron Zachary, MS,<sup>a,b</sup> Dong Joo Kim, MD,<sup>a</sup> Janelen Smith, MD,<sup>a</sup> and Hege Grande Sarpa, MD<sup>a,c</sup>  
*Irvine and Mission Viejo, California and Washington, DC*

**Key words:** CHILD syndrome; congenital hemidysplasia with ichthyosiform nevus and limb defects syndrome; congenital nevus; erythema; genodermatosis; hemidysplasia; limb defect; scaling; X-linked dominant.

## INTRODUCTION

Congenital hemidysplasia with ichthyosiform nevus and limb defects (CHILD) syndrome is an exceedingly rare, X-linked dominant genetic disorder of lipid metabolism that arises from mutations in NAD(P) dependent steroid dehydrogenase-like gene (*NSDHL*), which encodes  $3\beta$ -hydroxysteroid-dehydrogenase, an enzyme essential to cholesterol synthesis. Cholesterol plays a crucial role in hedgehog signaling during normal mammalian development, thus explaining the striking right-to-left unilateralism of both cutaneous and visceral manifestations typified by this condition. Presenting at birth or in the neonatal period, cutaneous findings are unilateral erythema and scaling that progress to increasingly hyperkeratotic, verrucous plaques or bands, sometimes Blaschkoid; partial spontaneous regression may occur over time. Skeletal defects, ranging from hypoplasia to complete amelia, and organ hypoplasia are likewise ipsilateral. CHILD syndrome is predominantly seen in females, as it is generally lethal in affected male embryos. In fact, there are currently only 2 reported cases in the literature of this disorder in males, one of whom we saw for follow-up nearly 20 years after his original description in 1996.<sup>1</sup> Here we provide an update on his clinical status and disease progression, as well as advances in the current understanding of disease pathogenesis and management of this rare condition.

### Abbreviations used:

CHILD:	Congenital hemidysplasia with ichthyosiform nevus and limb defects
CNS:	central nervous system
<i>NSDHL</i> :	NAD(P) dependent steroid dehydrogenase-like gene
SHH:	sonic hedgehog hormone

## CASE REPORT

A 24-year-old man with CHILD syndrome (*NSDHL* mutation c.262C>T, p.R88X)<sup>2,3</sup> presented for follow-up of right-sided, mildly pruritic, erythematous ichthyosiform nevus sparing the face. The overall area and distribution of involvement remained relatively stable over the years without much spread aside from slight expansion proportional to growth. He was treated in the past with topical corticosteroids, emollients, retinoids, and azole antifungals with minimal improvement. Dermabrasion of the affected areas on the trunk was gratifying initially but was ultimately nonsustained, with complete recurrence to original thickness within 8 months. The patient is currently undergoing treatment with a 2% simvastatin, 2% cholesterol compounded ointment applied twice daily to existing lesions with significant, sustained improvement.

The patient was born with a hypoplastic right leg lacking a fibula. Correctional attempts were made to salvage the lower leg, but he ultimately required

From the Department of Dermatology, the University of California, Irvine<sup>a</sup>; Georgetown University, School of Medicine<sup>b</sup>; and the Department of Dermatology, Southern California Kaiser Permanente Medical Group.<sup>c</sup>

Funding sources: None.

Conflicts of interest: None disclosed.

Correspondence to: Dong Joo Kim, MD, University of California Irvine, Department of Dermatology, 118 Med Surg 1, Irvine, CA 92697-2400. E-mail: [dongjok1@uci.edu](mailto:dongjok1@uci.edu).

JAAD Case Reports 2018;4:1010-3.  
 2352-5126

© 2018 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. All rights reserved. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jidcr.2018.10.001>



**Fig 1.** CHILD syndrome in a man. Right-sided congenital nevus with scaling and erythema involving the trunk (**A**) with Blaschkoid extension down the right anteromedial arm (**B**) and groin (**C**) extending down the ipsilateral thigh (**D**) in the setting of above-the-knee amputation for nonsalvageable lower limb defect.

above-the-knee amputation with no further complications. Otherwise, no organ hypoplasia was found at the time of initial description in 1996, with normal-sized heart, brain, eyes, and kidneys noted. Nearly 20 years later, the patient remained in good health overall without any chronic comorbid conditions or medications.

On examination, there was a well-margined nevus involving the right thigh, groin, abdomen

and chest extending down the right anteromedial arm along Blaschko lines (Fig 1). The affected areas on the thigh and groin were erythematous and thickened with waxy, yellowish scale, especially overlying the thigh. The affected areas on the abdomen and trunk were relatively clear in comparison, with faintly red-brown pigmentation and without significant hyperkeratosis or thickening. Periumbilically, to the right of midline, was a

geometric atrophic scar-like plaque, and around the right superior axillary fold was a curvilinear hyperkeratotic band with erythematous and verruciform accentuation centrally.

## DISCUSSION

CHILD syndrome is an X-linked dominant disorder of lipid metabolism that is usually lethal in males. As such, the prevalence of this disorder in males is exceedingly rare, as is the case in other X-linked dominant disorders, such as incontinentia pigmenti. For our patient, with normal 46, XY karyotype identified on peripheral blood mononuclear cell cytogenetic analysis, the proposed mechanism is an acquired, postzygotic mutation in *NSDHL* with subsequent mosaicism. Depending on the timing of his mutation, this may account for the complete lack of ipsilateral hemidysplasia of his internal organs, which tend to develop at earlier Carnegie stages relative to skeletal structures. Furthermore, the postzygotic mutation in our patient may have occurred between days 22 and 55 of development, allowing for initiation of central nervous system (CNS) and kidney embryogenesis but not fibula development. Interestingly, of the 33 reported cases of CHILD syndrome in the literature, only 5 had internal organ involvement beyond ipsilateral musculoskeletal hypoplasias.<sup>2-9</sup> The most common organs involved were the kidneys (3) and CNS (2), although lung, vocal cord, and auditory nerve involvement were also reported.

Specifically, a loss of function mutation in *NSDHL* (encoding 3 $\beta$ -hydroxysteroid-dehydrogenase) on Xq28 impairs cholesterol biosynthesis in the endoplasmic reticulum of keratinocytes.<sup>2,3</sup> Deficits in cholesterol cause a decrease in lamellar granules in the stratum corneum of the epidermis, leading to altered permeability of the skin characteristic of ichthyosis. Buildup of cholesterol precursors lead to reduced oxysterols and degeneration of HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase, further exacerbating the decrease in cholesterol production and subsequent epidermal disruption.<sup>4</sup> Impaired cholesterol biosynthesis also disrupts the functioning of sonic hedgehog hormone (SHH) in embryos, particularly in the development of the appendicular skeleton and central nervous system. Furthermore, signaling molecules in the SHH pathway are involved in dorsoventral axial patterning and left-right asymmetry. Buildup of harmful precursors of cholesterol synthesis contributes more to SHH dysfunction than does the lack of cholesterol itself, although both do contribute. This impairment explains the unilateral hypoplasias

sometimes seen in the CNS and limbs of patients with CHILD syndrome.<sup>10</sup>

Historical therapies for the cutaneous symptoms of CHILD syndrome include topical ointments (corticosteroids, emollients, retinoids, and azole antifungals such as ketoconazole<sup>11</sup>), oral agents (ketoconazole,<sup>11</sup> retinoids, and methotrexate), and surgical approaches (dermabrasion and skin grafting). These treatments have varying degrees of efficacy but do not address the underlying defect in cholesterol.<sup>4</sup> Skin grafting had been rather successful because the unaffected donor graft does not express the mutated allele and exhibits donor dominance.<sup>12</sup> However, this invasive approach can be costly and is not feasible in patients with nevi that take up large portions of their body surface. Today, treatment with topical 2% statin (lovastatin or simvastatin) and 2% cholesterol compounded ointment was found to be effective in 8 patients treated over 6 case reports. Twice-daily application for 6 months followed by 1 to 2 times weekly for maintenance produced marked improvement, with clinical improvement seen as early as 3 weeks into treatment.<sup>4-9</sup> This new pathogenesis-directed therapy is a cost-effective and noninvasive approach to treating the cutaneous manifestations of CHILD syndrome.

## REFERENCES

1. Happle R, Effendy I, Megahed M, Orlow SJ, Küster W. CHILD syndrome in a boy. *Am J Med Genet.* 1996;62(2):192-194.
2. König A, Happle R, Bornholdt D, Engel H, Grzeschik KH. Mutations in the *NSDHL* gene, encoding a 3 $\beta$ -hydroxysteroid dehydrogenase, cause CHILD syndrome. *Am J Med Genet.* 2000;90(4):339-346.
3. Bornholdt D, König A, Happle R, et al. Mutational spectrum of *NSDHL* in CHILD syndrome. *J Med Genet.* 2005;42(2):e17.
4. Paller AS, van Steensel MA, Rodriguez-Martín M, et al. Pathogenesis-based therapy reverses cutaneous abnormalities in an inherited disorder of distal cholesterol metabolism. *J Invest Dermatol.* 2011;131(11):2242-2248.
5. Bergqvist C, Abdallah B, Hasbani DJ, et al. CHILD syndrome: a modified pathogenesis-targeted therapeutic approach. *Am J Med Genet A.* 2018;176(3):733-738.
6. Alexopoulos A, Kakourou T. CHILD syndrome: successful treatment of skin lesions with topical simvastatin/cholesterol ointment—a case report. *Pediatr Dermatol.* 2015;32(4):e145-e147.
7. Christiansen AG, Koppelhus U, Sommerlund M. Skin abnormalities in CHILD syndrome successfully treated with pathogenesis-based therapy. *Acta Derm Venereol.* 2015;95(6):752-753.
8. Kiritsi D, Schauer F, Wölfe U, et al. Targeting epidermal lipids for treatment of Mendelian disorders of cornification. *Orphanet J Rare Dis.* 2014;9:33.
9. Bajawi SM, Jafarri SA, Buraik MA, Al Attas KM, Hannani HY. Pathogenesis-based therapy: cutaneous abnormalities of CHILD syndrome successfully treated with topical simvastatin monotherapy. *JAAD Case Rep.* 2018;4(3):232-234.

10. Stottmann RW, Turbe-Doan A, Tran P, et al. Cholesterol metabolism is required for intracellular hedgehog signal transduction in vivo. *PLoS Genet*. 2011;7(9):e1002224.
11. Liu T, Qian G, Wang XX, Zhang YG. CHILD syndrome: effective treatment of ichthyosiform naevus with oral and topical ketoconazole. *Acta Derm Venereol*. 2015;95(1):91-92.
12. König A, Skrzypek J, Löffler H, Oeffner F, Grzeschik KH, Happle R. Donor dominance cures CHILD nevus. *Dermatology*. 2010;220(4):340-345.